At paragraph 3 of the pending Office Action, the Examiner has requested an amendment of the specification to update the status of the priority documents. Applicants respectfully submit that the specification will be amended to update the status of the priority documents once the presently pending claims are indicated as allowable.

At paragraph 4 of the pending Office Action, the Examiner has requested the submission of formal drawings. Applicants respectfully submit that formal drawings will be submitted once the presently pending claims are indicated as allowable.

No new matter has been added. Any amendments to and/or cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and were done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Written Description Of The Pending Claims

Pursuant to the Examiner's request, Applicants respectfully submit that written description for: (A) "a method for inducing ex vivo proliferation of a population of T cells" may be found at, for example, page 2, lines 5-11 of U.S. Serial No. 08/253,964; (B) "covalently attached thereto" may be found at, for example, page 15, line 28 of U.S. Serial No. 08/253,964; (C) "first and second agents" may be found at, for example, page 2, lines 14-23 of U.S. Serial No. 08/253,964; (D) "a stimulatory form of a natural ligand of CD28 (e.g. B7-1) " may be found at, for example, page 7, lines 16-17 of U.S. Serial No. 08/253,964; (E) "monitoring proliferation, reactivating and restimulating T cells" may be found at, for example, page 42, lines 1-5 of U.S. Serial No. 08/253,964; and (F) "the recitation of claim 58" may be found at, for example, page 2, line 36, through page 3, line 1 of U.S. Serial No. 08/253,964.

Rejection of Claims 50-55 and 57 Under 35 U.S.C. § 102(b)

The Examiner has rejected claims 50-55 and 57 under 35 U.S.C. § 102(b) as being anticipated by Thompson *et al.* (WO 90/05541). The Examiner relies on Thompson *et al.* for

teaching methods of immunotherapy by stimulating T cells with immobilized anti-CD3 antibodies and anti-CD28 (see Examples III-VIII) and for teaching that "such methods are desirable for enhancing T cell immune responses directed specifically towards T cells activated by antigen (page 1-2, overlapping paragraph)." In particular, the Examiner is of the opinion that "[t]he claimed functional limitations would be inherent properties of the referenced methods."

Applicants respectfully traverse the aforementioned rejection for at least the following reasons. For a prior art reference to anticipate in terms of 35 U.S.C. § 102 a claimed invention, the prior art must teach ***each and every element*** of the claimed invention. Lewmar Marine v. Barient, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987).

Claim 50, and claims depending therefrom, are directed to a method for inducing *ex vivo* proliferation of a population of T cells by contacting a population of T cells *ex vivo* with a ***solid phase surface having covalently attached thereto***: (a) ***a first agent*** which provides a primary activation signal to the T cells, thereby activating the T cells; ***and*** (b) ***a second agent*** which stimulates an accessory molecule on the surface of the T cells, thereby stimulating the activated T cells, the first and second agents thereby inducing the population of T cells to proliferate.

Thompson *et al.*, teach methods of selectively regulating the *in vivo* level of a human T-cell lymphokine by administering a therapeutically effective amount of a ligand (*e.g.*, an anti-CD28 antibody) to a patient having a population of activated T cells. Thompson *et al.* do not teach or suggest methods for inducing a population of T cells to proliferate by contacting a population of T cells *ex vivo* with a ***solid phase surface having covalently attached thereto a first agent and a second agent***, as is required by Applicants' claims. Moreover, Thompson *et al.* teach away from the present invention by stating that "surprisingly, when the stimulation of the TCR/CD3 complex is maximized, upon costimulation with anti-CD28 ··· ***there is no significant increase*** in T cell proliferation over that induced by anti-CD3 alone" (see page 2, line 36 to page 3, line 3). Thus, Thompson *et al.* fail to teach or suggest the claimed invention and accordingly,

the Examiner is respectfully requested to reconsider and withdraw the foregoing section 102(b) rejection of claim 50 and claims depending therefrom.

Rejection of Claims 50-55, 57 and 58 Under 35 U.S.C. §103

The Examiner has rejected claims 50-55, 57 and 58 under 35 U.S.C. §103 as being unpatentable over Weiss *et al.* (1986) *J. Immunol.* 137: 819-825 and/or Ledbetter *et al.* (1985) *J. Immunol.* 135: 2331-2336, in view of "the art known use of covalently linking antibodies to solid phase to deliver stimulatory signals to cells of interest, including T cells as well as the art known practice to monitor cell proliferation of interest, including cell size and cell markers at the time the invention was made." The Examiner relies on Weiss *et al.* for teaching "stimulating proliferation in enriched T cells with immobilized anti-CD3 antibodies and saturating amounts of anti-Tp44 antibodies (i.e. anti-CD28) (see entire document; including Abstract, Results and Discussion)." The Examiner relies on Ledbetter *et al.* for teaching "augmenting and sustaining the proliferation in mononuclear cell populations which comprise T cells with immobilized anti-CD3 antibodies and anti-Tp44 antibodies (i.e. anti-CD28) (see entire document; including Abstract, Results and Discussion)." In particular, the Examiner is of the opinion that

> Weiss et al. teach that cross-linking of Tp44 molecules is required for stimulating T cells, given that Fab fragments of anti-Tp44 antibodies do not stimulate while F(ab')2 fragments (see Results and Discussion). Weiss et al. and Ledbetter et al. differ from the claimed methods by not disclosing the art known use of immobilized anti-CD28 antibodies in combination of anti-CD3 antibodies per se in the stimulation of T cells of interest at the time the invention was made. Given the art known use of applying immobilized antibodies to stimulate T cells, including the known use of anti-CD3 antibodies and multivalent forms /saturating amounts of anti-Tp44 (i.e. anti-CD28) antibodies to stimulate T cells, as taught by the teachings of Weiss et al. and Ledbetter et al.; one of ordinary skill in the art would have been motivated to stimulate antigen-specific T cells by covalently attaching both signals of anti-CD3 antibodies and anti-CD28 antibodies as a convenient and art known means to deliver said stimulatory signals to T cells ex vivo / in vitro. For example, it was known to provide such stimulatory signals by covalently linking the antibodies to plastic surfaces, as taught by Weiss et al. and Ledbetter et al. or via other convenient solid phase surfaces such as microbeads,

as known and commercially available at the invention was made. It was readily understood and practiced by the ordinary artisan at the time the invention was made that by covalently linking such stimulatory agents to solid phase; the activated cells of interest would have been readily separated from the culture and agents and isolated accordingly. Similarly, it was an art known practice to monitor cell proliferation of interest, including cell size and cell markers at the time the invention was made; as such criteria were known parameters of cell activation. Also, it was common practice at the time the invention was made to re-activate and re-stimulate cells to maintain proliferation and expansion of cell populations of interest at the time the invention was made. Therefore, one of ordinary art at the time the invention was made would have expected to monitor the proliferation of said T cells by various parameters and to re-stimulate T cells undergoing expansion to achieve large number of cells of interest. One of ordinary skill in the art at the time the invention was made would have been motivated to stimulate T cell activation with both CD3-/CD28-specific antibodies, including covalently linking both stimuli to solid phase surfaces, to increase T cell proliferation and numbers of T cells of interest for various purposes, such as T cell studies and adoptive immunotherapy. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicants respectfully traverse the Examiner's assertion that the claimed invention would have been obvious to the skilled artisan at the time it was made. Reconsideration and withdrawal of the rejection in light of the following discussion is respectfully requested.

Claim 50, and claims depending therefrom, are directed to a method for inducing *ex vivo* proliferation of a population of T cells by contacting a population of T cells *ex vivo* with a ***solid phase surface having covalently attached thereto***: (a) ***a first agent*** which provides a primary activation signal to the T cells, thereby activating the T cells; ***and*** (b) ***a second agent*** which stimulates an accessory molecule on the surface of the T cells, thereby stimulating the activated T cells, the first and second agents thereby inducing the population of T cells to proliferate.

To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary

skill in the art would have been motivated to make the claimed invention and would have had a reasonable expectation of success in making the claimed invention. Under section 103, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.,* 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)). Moreover, when a combination of references are used to establish a *prima facie* case of obviousness, the Examiner must present evidence that one having ordinary skill in the art would have been motivated to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention. See, e.g., *Carella v. Starlight Archery*, 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); and *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985).

Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness. The first reference relied upon by the Examiner, Weiss *et al.*, teach that soluble monoclonal antibody 9.3, "which recognizes a 90,000 dalton homodimer expressed on human T cells, synergizes with ligands reacting with T3/Ti to activate purified T cells and Jurkat, a human T cell leukemic line" (see the abstract at page 819). Contrary to the Examiner's assertions, Weiss *et al.* fail to provide the motivation to combine the teachings of Weiss *et al.* with the general knowledge in the art at the time the invention was made to arrive at the claimed invention. Weiss *et al.* merely disclose that the Tp44 monoclonal antibody can substitute for PMA in the mitogenic response of T cells to immobilized anti-T3 antibody. Weiss *et al.* state that the physiologic ligand for Tp44 is unknown (see, *e.g.*, at page 824, last paragraph). Weiss *et al.* fail to teach or suggest methods for inducing a population of T cells to proliferate by contacting a population of T cells *ex vivo* with a ***solid phase surface having covalently attached thereto a first agent and a second agent***, as is required by Applicants' claims.

Similarly, Ledbetter *et al.* report the results of a comparative experiment, where macrophage-depleted T cells were contacted with immobilized anti-CD3 antibodies and soluble anti-TP44 and anti-Tp67 antibodies (see in particular, the first paragraph on the left hand side

column at page 2333). Thus, Ledbetter *et al.* also fails to teach or suggest methods for inducing a population of T cells to proliferate by contacting a population of T cells *ex vivo* with a ***solid phase surface having covalently attached thereto a first agent and a second agent***, as is required by Applicants' claims.

In view of the foregoing, the proposed combination of references fails to teach or suggest (either explicitly or implicitly) Applicants' claimed invention.

In addition, Applicants wish to address the Examiner's position that "one of ordinary skill in the art would have been motivated to stimulate antigen-specific T cells by covalently attaching both signals of anti-CD3 antibodies and anti-CD28 antibodies as a convenient and art known means to deliver said stimulatory signals to T cells ex vivo / in vitro."

Applicants respectfully submit that, contrary to these assertions, the ordinarily skilled artisan at the time of Applicants' invention would not have been motivated nor have reasonably expected to succeed in covalently immobilizing the first agent, *e.g.*, an anti-CD3 antibody, and the second agent, *e.g.*, an anti-CD28 antibody, ***on the same solid phase*** for at least the following reasons. To begin with, the prior art (as evidenced by Ledbetter *et al. J. Immunol.*, 1985, cited by the Examiner) taught that ***soluble anti-CD28 antibodies*** in combination with immobilized anti-CD3 antibodies could ***efficiently induce a population of T cells to proliferate***. Thus, an ordinarily skilled artisan would not have been motivated to immobilize the anti-CD28 antibody, much the less immobilize it on the same solid phase surface as the anti-CD3 antibody.

In addition, the prior art taught that co-immobilization (*i.e.*, immobilization on the same solid phase) of anti-CD3 antibodies and a second agent which delivers an activation signal would inhibit rather than augment the desired effect. For example, Ledbetter J.A. *et al.* show that T cell proliferation initiated by immobilized anti-CD3 ***was inhibited by anti-CD45 when immobilized on the same solid phase***, but not when in solution (see Ledbetter J.A. *et al.*, a copy of which is attached herein as Appendix B, in particular the abstract on page 8628). Thus, an ordinarily skilled artisan would not have the necessary motivation to make Applicants' invention, *i.e.*, to covalently immobilize the first agent, *e.g.*, an anti-CD3 antibody, and the second agent,

e.g., an anti-CD28 antibody on the same solid phase surface, nor have reasonably expected to succeed in doing so.

For the foregoing reasons, rejection of claim 50 and claims depending therefrom under 35 U.S.C. §103 is believed to be improper and Applicants respectfully request that it be withdrawn.

Rejection of Claims 50-55, 57 and 58 Under 35 U.S.C. §103

The Examiner has rejected claims 50-55, 57 and 58 under 35 U.S.C. § 103 as being unpatentable over Weiss *et al.* and/or Ledbetter *et al.* in view of Zarling *et al.* (U.S. Patent No. 5,081,029). The Examiner relies on Weiss *et al.* and Ledbetter *et al.* for the reasons set forth above. The Examiner relies on Zarling *et al.* for providing "the known motivation to stimulate and grow large number of T cells at the time the invention was made." In particular, the Examiner is of the opinion that

> Zarling et al. teach methods of adoptive immunotherapy for treating various disorders, including stimulating antigen-specific T cells comprising CD3+ T cells, including the use of various stimuli including antiTp44 antibodies (column 7, paragraphs 1-2) for the expansion of T cells for adoptive immunotherapy(see entire document, including Summary of the Invention, Detailed Description of the Invention, Isolation, Activation and Expansion of Lymphocytes, including Examples). Therefore, one of ordinary art at the time the invention was made would have expected to monitor the proliferation of said antigen-specific T cells, to re-stimulate T cells undergoing expansion to achieve large number of cells (e.g. 100-100,000-fold) required for adoptive immunotherapy. One of ordinary skill in the art at the time the invention was made would have been motivated to stimulate T cell activation with both CD3-/CD28-specific antibodies, including covalently linking both stimuli to solid phase surfaces, to increase T cell proliferation and numbers of T cells of interest for various purposes, such as T cell studies and adoptive immunotherapy. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicants respectfully traverse the Examiner's assertion that the claimed invention would have been obvious to the skilled artisan at the time it was made. Reconsideration and withdrawal of the rejection in light of the following discussion is respectfully requested. Applicants reiterate here the substance of the remarks set forth above with respect to the section 103 rejection of claims 50-55, 57 and 58 over Weiss *et al.* and Ledbetter *et al.* Briefly, Applicants respectfully submit that neither Weiss *et al.* nor Ledbetter *et al.* teach or suggest methods for inducing a population of T cells to proliferate by contacting a population of T cells *ex vivo* with a ***solid phase surface having covalently attached thereto a first agent and a second agent***, as is required by Applicants' claims. Thus, the proposed combination of references fails to teach or suggest the claimed invention.

Moreover, the secondary reference relied on by the Examiner, namely Zarling *et al.*, does not make up for the deficiencies in the primary references. Specifically, Zarling *et al.*, teach expansion of activated T lymphocytes ***by exposure to AIDS virus-related epitopes***. In a long list of molecules, which can be used for such a purpose, antibodies that recognize the Tp67 or Tb44 antigens on T cells are mentioned. Nowhere do Zarling *et al.* teach or suggest methods for inducing a population of T cells to proliferate by contacting a population of T cells *ex vivo* with a ***solid phase surface having covalently attached thereto a first agent and a second agent***.

In view of the foregoing, the proposed combination of references fails to teach or suggest (either explicitly or implicitly) Applicants' claimed invention. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing 35 U.S.C., section 103 rejection of claim 50 and claims depending therefrom.

Rejection of Claims 50-55, 57 and 58 Under 35 U.S.C. §103

The Examiner has rejected claims 50-55, 57 and 58 under 35 U.S.C. §103 as being unpatentable Thompson *et al.* in view of "the art known use of covalently linking antibodies to solid phase to deliver stimulatory signals to cells of interest, including T cells as well as the art known practice to monitor cell proliferation of interest, including cell size and cell markers at the

time the invention was made." The Examiner relies on Thompson *et al.* for teaching "methods of immunotherapy by stimulating T cells with immobilized anti-CD3 antibodies and anti-CD28 (see Examples III-VIII)" and for teaching that "such methods are desirable for enhancing T cell immune responses directed specifically towards T cells activated by antigen (see entire document, including page 1-2, overlapping paragraph)." In particular, the Examiner is of the opinion that

> Thompson et al. differs from the claimed methods by not explicitly teaching covalently linking anti-CD28 antibodies per se and the monitoring of stimulated T cell populations by the claimed limitations per se. However, it is noted that Thompson et al. clearly teach monitoring various markers of activation (see entire document, including Examples). Given the art known use of applying immobilized antibodies to stimulate T cells, including the known use of anti-CD3 antibodies and multivalent forms of anti-Tp44 (i.e. anti-CD28) antibodies to stimulate T cells, as taught by the teachings of Thompson et al; one of ordinary skill in the art would have been motivated to stimulate antigen-specific T cells by covalently attaching both signals of anti-CD3 antibodies and anti-CD28 antibodies as a convenient and art known means to deliver said stimulatory signals to T cells ex vivo / in vitro. For example, it was known to provide such stimulatory signals by covalently linking the antibodies to plastic surfaces, as taught by Weiss et al. and Ledbetter et al. or via other convenient solid phase surfaces such as microbeads, as known and commercially available at the time the invention was made. It was readily understood and practiced by the ordinary artisan at the time the invention was made that by covalently linking such stimulatory agents to solid phase; the activated cells of interest would have been readily separated from the culture and agents and isolated accordingly. It was an art known practice to monitor cell proliferation of interest, including cell size and cell markers at the time the invention was made; as such criteria were known parameters of cell activation. Also, it was common practice at the time the invention was made to re-activate and re-stimulate cells to maintain proliferation and expansion of cell populations of interest at the time the invention was made. Therefore, one of ordinary art at the time the invention was made would have expected to monitor the proliferation of said T cells by various parameters and to re-stimulate T cells undergoing expansion to achieve large number of cells of interest.

Applicants respectfully traverse the Examiner's assertion that the claimed invention would have been obvious to the skilled artisan at the time it was made. Reconsideration and withdrawal of the rejection in light of the following arguments is respectfully requested.

Applicants reiterate here the substance of the remarks set forth above with respect to the section 102 rejection of claims 50-55, 57 and 58 over Thompson *et al.* Briefly, Applicants respectfully submit that Thompson *et al.* do not teach or suggest methods for inducing a population of T cells to proliferate by contacting a population of T cells *ex vivo* with a ***solid phase surface having covalently attached thereto a first agent and a second agent***, as is required by Applicants' claims.

Moreover, as indicated above, contrary to the Examiner's assertions, the ordinarily skilled artisan at the time of Applicants' invention would not have been motivated nor have reasonably expected to succeed in covalently immobilizing the first agent, *e.g.*, an anti-CD3 antibody, and the second agent, *e.g.*, an anti-CD28 antibody, ***on the same solid phase*** because the prior art taught that: (1) ***soluble anti-CD28 antibodies*** in combination with immobilized anti-CD3 antibodies could ***efficiently induce a population of T cells to proliferate*** and (2) co-immobilization (*i.e.*, immobilization on the same solid phase) of anti-CD3 antibodies and a second agent which delivers an activation signal would ***inhibit rather than augment the desired effect of inducing a population of T cells to proliferate***. Thus, an ordinarily skilled artisan would not have the necessary motivation to make Applicants' invention, *i.e.*, to covalently immobilize the first agent and the second agent on the same solid phase surface, nor have reasonably expected to succeed in doing so.

For the foregoing reasons, rejection of claim 50 and claims depending therefrom under 35 U.S.C. §103 is believed to be improper and Applicants respectfully request that it be withdrawn.

Provisional Rejection of Claims 50-55, 57 and 58 Under The Judicially Created Doctrine Of Obviousness-type Double Patenting

The Examiner has provisionally rejected claims 50-55, 57 and 58 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 52, 62, 65, 80, 81, 84, 86, 88, 90, 92, 94, 95, 98, 99 and 102 of commonly assigned copending USSN 08/403,253 and claims 1, 46, 47, 50, 51, 52, 56-58 and 71 of commonly assigned copending USSN 09/183,055. The Examiner is of the opinion that "[a]lthough the conflicting claims are not identical, they are not patentably distinct from each other because the instant and copending claims appear to rely upon the same or nearly the same method steps and ingredients, particularly the use of anti-CD3 and anti-CD28 antibodies to stimulate and expand T cells, including CD8+ T cells."

While in no way admitting that claims 50-55, 57 and 58 are obvious over claims 52, 62, 65, 80, 81, 84, 86, 88, 90, 92, 94, 95, 98, 99 and 102 of co-pending application Serial Number 08/403,253 and claims 1, 46, 47, 50, 51, 52, 56-58 and 71 of co-pending application Serial Number 09/183,055, upon allowance of the claims in the '253 or '055 applications, Applicants will consider submitting a terminal disclaimer in compliance with 37 C.F.R. 1.321(b) and (c), if appropriate, which will obviate this rejection.

Rejection of Claims 50-55, 57 and 58 Under 35 U.S.C. § 102(f) or (g)

The Examiner is of the opinion that "[c]laims 50-55, 57 and 58 are directed to an invention not patentably distinct from claims 52, 62, 65, 80, 81, 84, 86, 88, 90, 92, 94, 95, 98, 99 and 102 of commonly assigned copending USSN 08/403,253 and claims 1, 46, 47, 50, 51, 52, 56-58 and 71 of commonly assigned copending USSN 09/183,055."

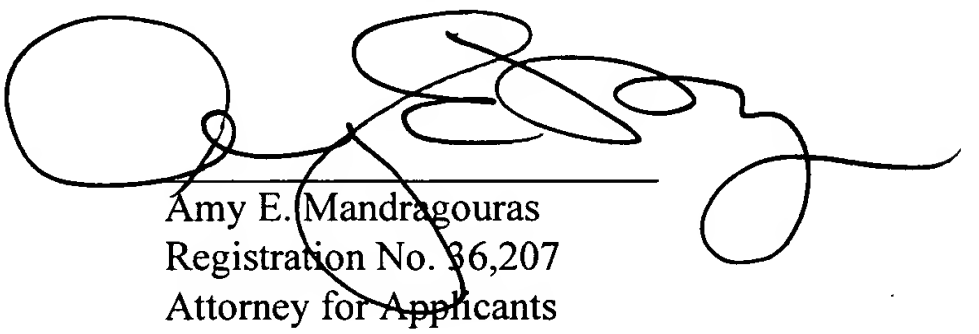
Without acquiescing to the rejection and if deemed necessary, Applicants will consider submitting a declaration under 37 CFR §1.132 which will indicate that the Applicants of the instant patent application conceived and invented the subject matter disclosed in U.S.

Application Serial No. 09/183,055 and U.S. Application Serial No. 08/403,253 and relied on in the Examiner's rejection, as required by M.P.E.P. §715.01(a). *In re DeBaum*, 687 F.2d 459, 214 *USPQ* 933 (CCPA 1982). The filing of such a declaration will obviate the foregoing rejection.

CONCLUSION

Reconsideration and allowance of all the pending claims is respectfully requested. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,



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Dated: May 18, 2001

APPENDIX A

50. A method for inducing *ex vivo* proliferation of a population of T cells, comprising:

contacting a population of T cells *ex vivo* with a solid phase surface having covalently attached thereto:

(a) a first agent which provides a primary activation signal to the T cells, thereby activating the T cells; and

(b) a second agent which stimulates an accessory molecule on the surface of the T cells, thereby stimulating the activated T cells,

the first and second agents thereby inducing the population of T cells to proliferate.

51. The method of claim 50, wherein the first agent stimulates a TCR/CD3 complex-associated signal in the T cells.

52. The method of claim 50, wherein the first agent is an anti-CD3 antibody.

53. The method of claim 52, wherein the anti-CD3 antibody is an anti-human CD3 monoclonal antibody.

54. The method of claim 50, wherein the accessory molecule on the T cell is CD28.

55. The method of claim 54, wherein the second agent is an anti-CD28 antibody.

56. The method of claim 54, wherein the second agent is a stimulatory form of a natural ligand of CD28.

57. The method of claim 50, further comprising:

monitoring proliferation of the T cells; and

reactivating and re-stimulating the T cells with the first and second agents when the rate of T cell proliferation has decreased to induce further proliferation of the T cells.

58. The method of claim 57, wherein the step of monitoring proliferation of the T cells is by examining cells size or determining the level of expression of a cell surface molecule,

and the step of reactivating and re-stimulating is initiated when T cell size has decreased or when the level of the cell surface molecule has decreased.

59. The method of claim 58, wherein the cell surface molecule is B7-1.